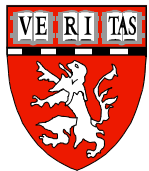# ICH – SECONDARY PREVENTION…

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Disclosures

- NIH/NINDS
  - U01 NS 074425

    Futility study of deferoxamine mesylate in ICH

- AHA Collaborative Sciences Award
  - 15CSA24540001

    Injectable Biomaterial Matrix for Hemorrhagic

    Stroke: Mechanisms and Therapies

AHA/ASA Guideline

Guidelines for the Management of Spontaneous Intracerebral Hemorrhage

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.

Endorsed by the American Association of Neurological Surgeons, the Congress of Neurological Surgeons, and the Neurocritical Care Society

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Objectives

To Discuss:

- The epidemiology of ICH recurrence

- Importance of preventing ICH recurrence

- Secondary preventive strategies
  - BP Control
  - Judicious use of anti-thrombotic agents
    - Antiplatelets
    - Anticoagulants
  - Judicious use of statins

Epidemiology

o ICH survivors are at high risk for a recurrent event

o The cumulative risk of ICH recurrence varies from 1% to 5% per year

o In PROGRESS, the risk of ICH recurrence in patients with ICH was higher than the risk of a first ICH in IS patients (HR = 6.5; 95% CI 4.5 – 9.7)

o The risk of ICH recurrence is ongoing and extends for years especially in patients with lobar ICH, i.e. the frequency of recurrent ICH does not seem to significantly decline over time

Epidemiology – Risk Factors

The risk factors for ICH recurrence are:

- Location of the initial ICH (lobar vs. deep)
    - Annual risk for ICH recurrence after deep ICH ~ 2% to 3%
    - Annual risk for ICH recurrence after lobar ICH ~ 7% to 14%

- HTN
    - High BP increases the recurrence of both deep & lobar ICH
    - The only known intervention for secondary prevention of ICH is lowering BP

- Older age
    - Higher prevalence of CAA
    - Increased use of anti-thrombotic drugs

Epidemiology – Risk Factors

o Carriers of APO-E ε2 or ε4 genotype

o Greater number of microbleeds (especially in lobar locations) on GRE or T2* MRI

o Detection of superficial siderosis on MRI

o Patients with recurrent ICHs

o Race:
   o In Whites, most of the initial & recurrent ICHs tend to be lobar
   o In Asians, deep ICHs tend to be more common

Prerequisites of Secondary Prevention

Identification of the etiology/mechanism of the initial ICH is an important first step. It allows:

- Stratification of the risk of ICH recurrence

- Tailoring of preventive strategies to decrease the risk of recurrence

Secondary Prevention of ICH: Why Not?

- ICH is a frequent cause of morbidity and mortality
  - Mortality up to 40%
  - Most patients are left with serious and permanent disability

- Is it really worth the cost and resources to prevent ICH recurrence?

Secondary Prevention of ICH: Why YES?

- Up to 30% of ICH patients achieve mRS ≤2 by 90 days, and slightly more by 6 months!

- 70,000 patients are admitted with ICH to hospitals in the United States & 400,000 in the Far East each year

- Worldwide, the overall incidence of ICH is approximately 25 per 100,000 person years

BP Management

- ❖ Inappropriate BP control increases risk of ICH recurrence
- ❖ Adequate control of BP reduces risk of ICH recurrence

Long-term BP control is inadequate in ICH patients…

Poor Long-Term Blood Pressure Control After Intracerebral Hemorrhage

Darin B. Zahuranec, MD, MS; Jeffrey J. Wing, MPH; Dorothy F. Edwards, PhD; Ravi S. Menon, MD;
Stephen J. Fernandez, MPH; Richard E. Burgess, MD, PhD; Ian A. Sobotka, BS; Laura German, BS;
Anna J. Trouth, MD; Nawar M. Shara, PhD; M. Chris Gibbons, MD, MPH;
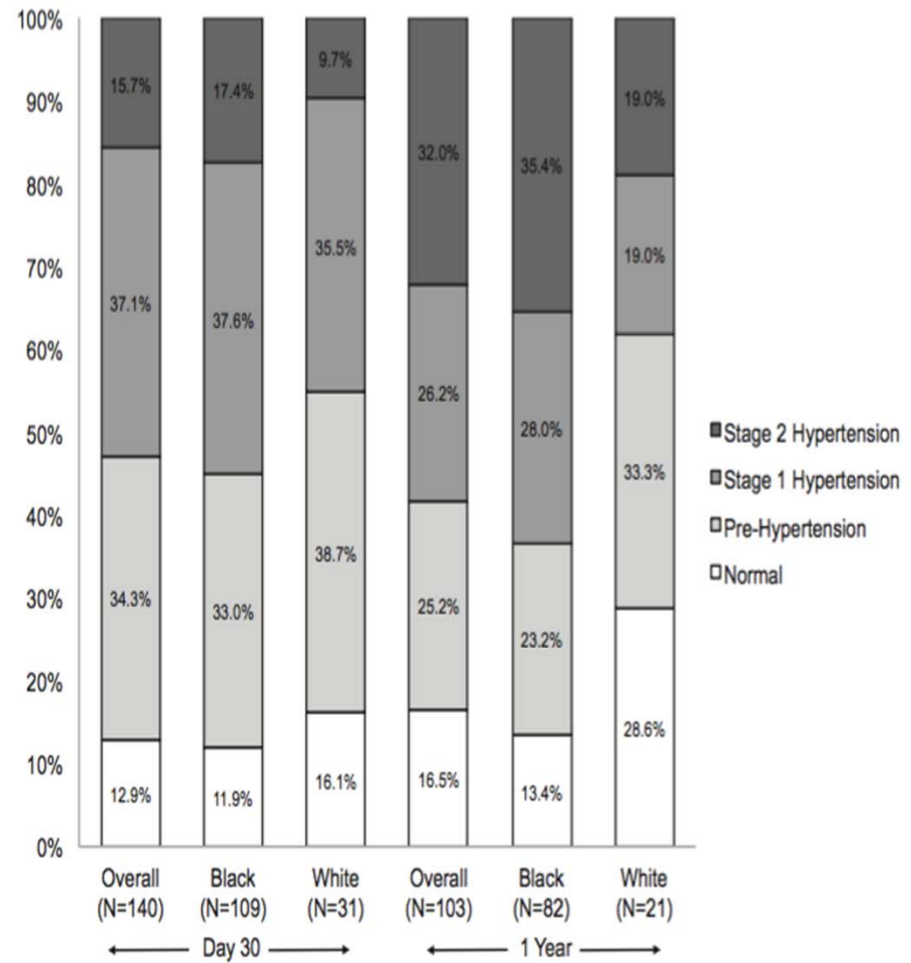Bernadette Boden-Albala, MPH, DrPH; Chelsea S. Kidwell, MD

Background and Purpose—Hypertension is the most important risk factor associated with intracerebral hemorrhage. We explored racial differences in blood pressure (BP) control after intracerebral hemorrhage and assessed predictors of BP control at presentation, 30 days, and 1 year in a prospective cohort study.

Methods—Subjects with spontaneous intracerebral hemorrhage were identified from the DiffErenCes in the Imaging of Primary Hemorrhage based on Ethnicity or Race (DECIPHER) Project. BP was compared by race at each time point. Multivariable linear regression was used to determine predictors of presenting mean arterial pressure, and longitudinal linear regression was used to assess predictors of mean arterial pressure at follow-up.

Results—A total of 162 patients were included (mean age, 59 years; 53% male; 77% black). Mean arterial pressure at presentation was 9.6 mm Hg higher in blacks than whites despite adjustment for confounders ($P=0.065$). Fewer than 20% of patients had normal BP (<120/80 mm Hg) at 30 days or 1 year. Although there was no difference at 30 days ($P=0.331$), blacks were more likely than whites to have Stage I/II hypertension at 1 year ($P=0.036$). Factors associated with lower mean arterial pressure at follow-up in multivariable analysis were being married at baseline ($P=0.032$) and living in a facility (versus personal residence) at the time of BP measurement ($P=0.023$).

Conclusions—Long-term BP control is inadequate in patients after intracerebral hemorrhage, particularly in blacks. Further studies are needed to understand the role of social support and barriers to control to identify optimal approaches to improve BP in this high-risk population. (*Stroke.* 2012;43:2580-2585.)

Key Words: hypertension ■ intracerebral hemorrhage ■ secondary prevention ■ racial differences

Figure (stacked bar chart), legend: Stage 2 Hypertension, Stage 1 Hypertension, Pre-Hypertension, Normal

	Overall (N=140)	Black (N=109)	White (N=31)	Overall (N=103)	Black (N=82)	White (N=21)
Stage 2 Hypertension	15.7%	17.4%	9.7%	32.0%	35.4%	19.0%
Stage 1 Hypertension	37.1%	37.6%	35.5%	26.2%	28.0%	19.0%
Pre-Hypertension	34.3%	33.0%	38.7%	25.2%	23.2%	33.3%
Normal	12.9%	11.9%	16.1%	16.5%	13.4%	28.6%

Day 30 (Overall, Black, White) — 1 Year (Overall, Black, White)

Inadequate BP control is associated with higher risk for ICH recurrence…

- 1145 ICH patients
- Median follow-up = 36.8 months (minimum = 9.8)
- <50% of patients achieved consistent BP control in line with AHA/ASA guidelines
- Recurrence:
  - 102/505 among survivors of lobar ICH (~ 20%)
    - 84 vs. 49 per 1000 person-years among patients with inadequate BP control compared with adequate BP control
    - HR 3.53 (95% CI 1.65-7.54)
  - 44/640 among survivors of non-lobar (~ 7%)
    - 52 vs. 27 per 1000 person-years among patients with inadequate BP control compared with adequate BP control
    - HR 4.23 995% CI 1.02-17.52)

Biffi et al. JAMA. 2015;314(9):904-912

- All hypertensive stages above normotension (90-119/60-79 mmHg) were associated with increased risk for ICH recurrence

- HR for lobar ICH (1.33; 95% CI 1.02-1.76) and non-lobar ICH (1.54; 95% CI 1.03-2.30) per 10 mmHg increase in BP

- Both elevated SBP & DBP are associated with increased risk of ICH recurrence
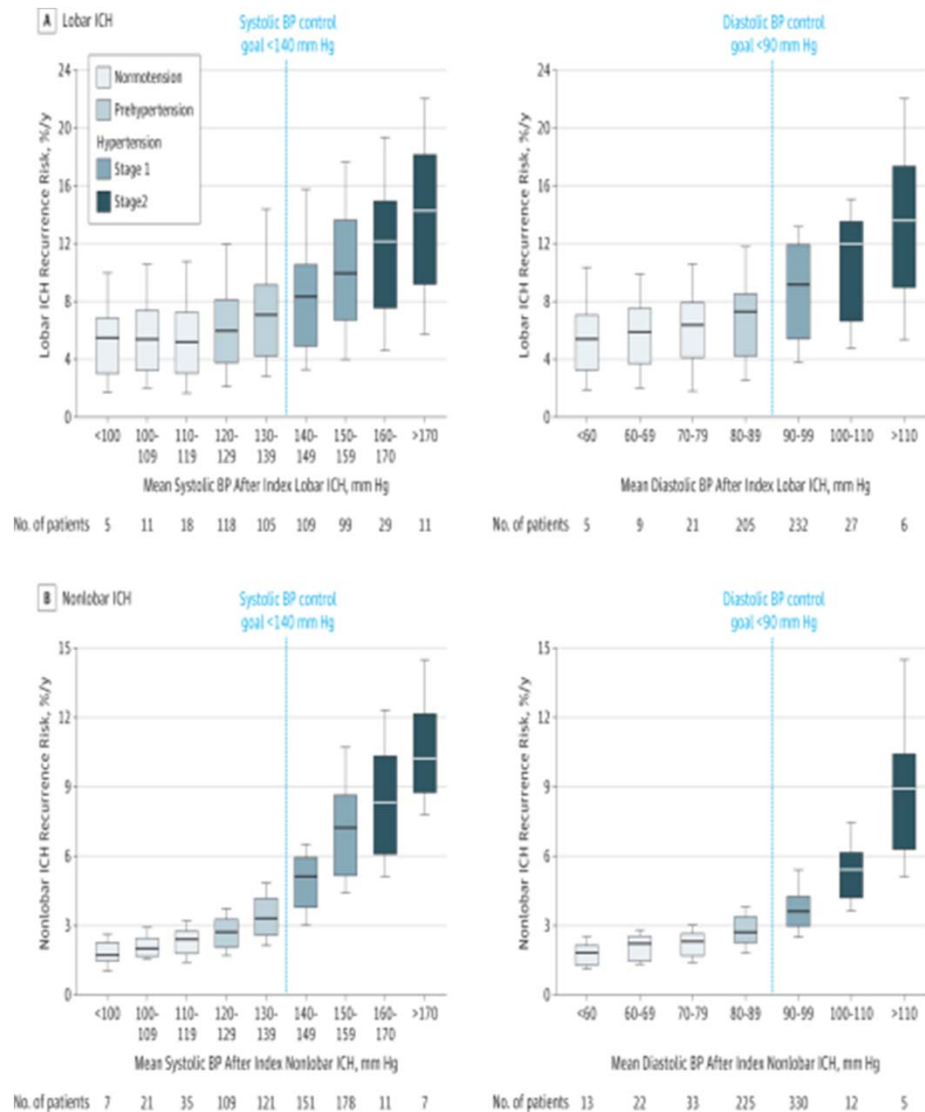
BP lowering is beneficial in ICH survivors PROGRESS

- 6015 patients with history of IS, TIA, or ICH were randomized to perindopril w/ or w/o indapamide or placebo

- Mean follow-up ~ 3.9 years

- Mean difference in BP between active treatment & placebo was 9/4 mm Hg
  - 12/5 mmHg with combination therapy
  - 5/3 mmHg with single-drug therapy

- Overall stroke risk reduction with active treatment was 28% (95% CI 17-38)
  - RRR 43% with combination therapy
  - RRR 5% with single therapy

Lancet. 2001; 358:1033–1041

BP lowering is beneficial across all stroke types, particularly ICH

Effects of a Perindopril-Based Blood Pressure–Lowering Regimen on the Risk of Recurrent Stroke According to Stroke Subtype and Medical History
The PROGRESS Trial

N. Chapman, MRCP; R. Huxley, DPhil; C. Anderson, PhD; M. G. Bousser, MD;
J. Chalmers, MD, PhD; S. Colman; S. Davis, MD; G. Donnan, MD, FRACP, FRCP;
S. MacMahon, PhD; B. Neal, PhD; C. Warlow, MD; M. Woodward, PhD

Background and Purpose—The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) showed that blood pressure lowering reduced stroke risk in patients with a history of cerebrovascular events. Here, we report the consistency of treatment effects across different stroke subtypes and among major clinical subgroups.

Methods—PROGRESS was a randomized, double-blind trial among 6105 people with a prior history of cerebrovascular events. Participants were assigned to active treatment (perindopril for all participants and indapamide for those with neither an indication for nor a contraindication to a diuretic) or matching placebo(s).
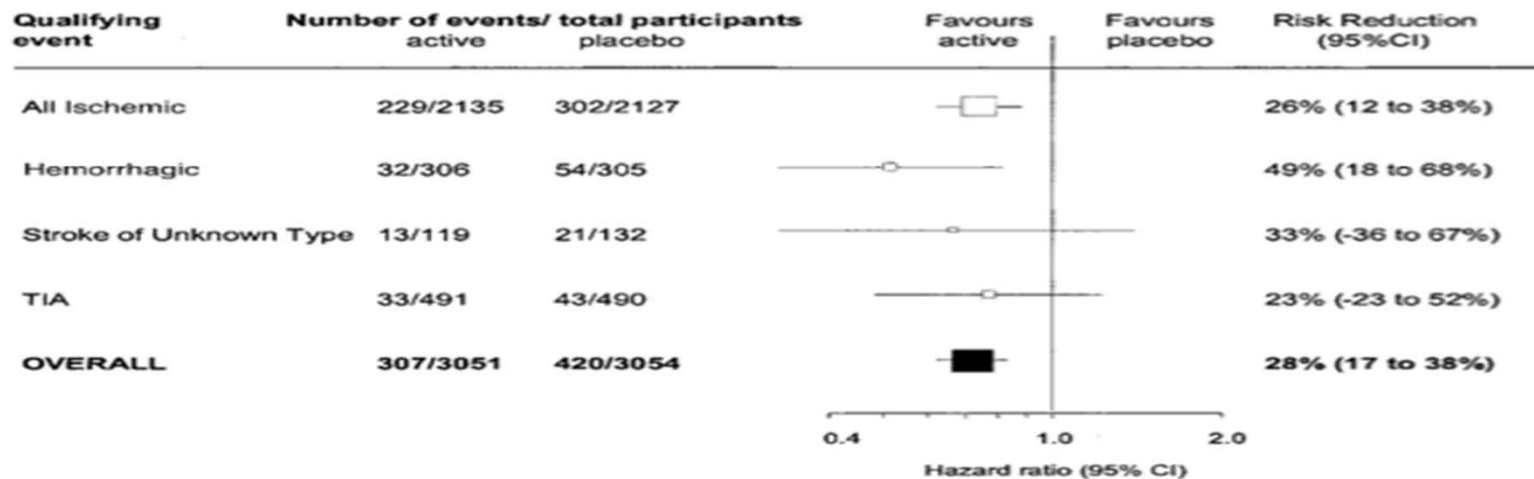
Results—During a mean of 3.9 years of follow-up, active treatment reduced the absolute rates of ischemic stroke from 10% to 8% (relative risk reduction [RRR], 24%; 95% confidence interval [CI], 10 to 35) and the absolute rates of intracerebral hemorrhage from 2% to 1% (RRR, 50%; 95% CI, 26 to 67). The relative risk of any stroke during follow-up was reduced by 26% (95% CI, 12 to 38) among patients whose baseline cerebrovascular event was an ischemic stroke and by 49% (95% CI, 18 to 68) among those whose baseline event was an intracerebral hemorrhage. There was no evidence that treatment effects were modified by other drug therapies (antiplatelet or other antihypertensive agents), residual neurological signs, atrial fibrillation, or the time since the last cerebrovascular event.

Conclusions—Beneficial effects of a perindopril-based treatment regimen were observed for all stroke types and all major clinical subgroups studied. These data suggest that effective blood pressure–lowering therapy should be routinely considered for all patients with a history of cerebrovascular events. (*Stroke*. 2004;35:116-121.)

○ 727 participants had 886 strokes during follow up
  ○ 656 ischemic
  ○ 123 ICH
  ○ 107 unknown type

○ Risk of IS was reduced in the active treatment group by 24% (95% CI 10-35)

○ RRR of ICH was 50% (95% CI 26-67)
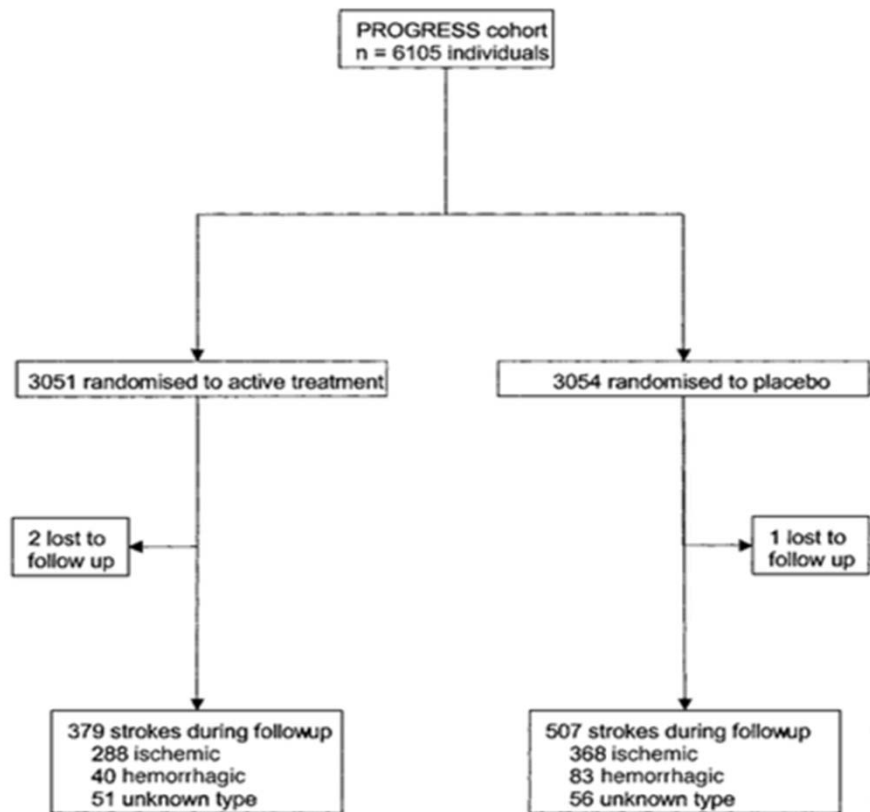
- ~ 11% of participants in each arm had a history of ICH
  - Overall, active treatment reduced absolute rates of ICH from 2% to 1% (RRR 50%; 95% CI 26-67%) during a mean follow-up of 3.9 years
  - RRR was 76% with combination therapy and -1% with single therapy
  - 50% of recurrent strokes were hemorrhagic & 35% ischemic
  - RRR for stroke among patients with a baseline ICH was 49% (95% CI 18-68)

Qualifying event	Number of events/ total participants active	placebo	Favours active	Favours placebo	Risk Reduction (95%CI)
All Ischemic	229/2135	302/2127			26% (12 to 38%)
Hemorrhagic	32/306	54/305			49% (18 to 68%)
Stroke of Unknown Type	13/119	21/132			33% (-36 to 67%)
TIA	33/491	43/490			23% (-23 to 52%)
OVERALL	307/3051	420/3054			28% (17 to 38%)

0.4   1.0   2.0

Hazard ratio (95% CI)

Effects of Perindopril-Based Lowering of Blood Pressure on Intracerebral Hemorrhage Related to Amyloid Angiopathy
The PROGRESS Trial

Hisatomi Arima, MD; Christophe Tzourio, MD; Craig Anderson, MD; Mark Woodward, PhD;
Marie-Germaine Bousser, MD; Stephen MacMahon, PhD; Bruce Neal, MD; John Chalmers, MD;
for the PROGRESS Collaborative Group

Background and Purpose—Patients with cerebral amyloid angiopathy (CAA) are at high risk for intracerebral hemorrhage (ICH), but no effective prevention strategies have been established. The objective is to determine whether lowering of blood pressure (BP) provides protection for this high-risk patient group.

Methods—This study is a subsidiary analysis of the PROGRESS trial—a randomized, placebo-controlled trial that established the beneficial effects of BP lowering in patients with cerebrovascular disease; 6105 patients were randomly assigned to either active treatment (perindopril for all participants plus indapamide for those with neither an indication for nor a contraindication to a diuretic) or matching placebo. Outcomes were probable CAA-related ICH as defined by the Boston criteria, probable hypertension-related ICH, and unclassified ICH.

Results—Over a mean follow-up of 3.9 years, 16 probable CAA-related ICH, 51 probable hypertension-related ICH, and 44 unclassified ICH occurred. Active treatment reduced the risk of CAA-related ICH by 77% (95% CI, 19%–93%), that of hypertension-related ICH by 46% (95% CI, 4%–69%), and that of unclassified ICH by 43% (95% CI, −5%–69%). There was no evidence of differences in the magnitude of the effects of treatment among different types of ICH (P homogeneity=0.4).

Conclusions—BP-lowering treatment is likely to provide protection against all types of ICH. (*Stroke*. 2010;41:394-396.)

Lowering BP is beneficial across all ICH subtypes…

- 88% of patients with CAA-related ICH had pre-existing ICH
- 84% of patients with HTN-related ICH had pre-existing IS
- Active treatment reduced risk of CAA-ICH by 77%, HTN-ICH by 46%, and unclassified ICH by 43%
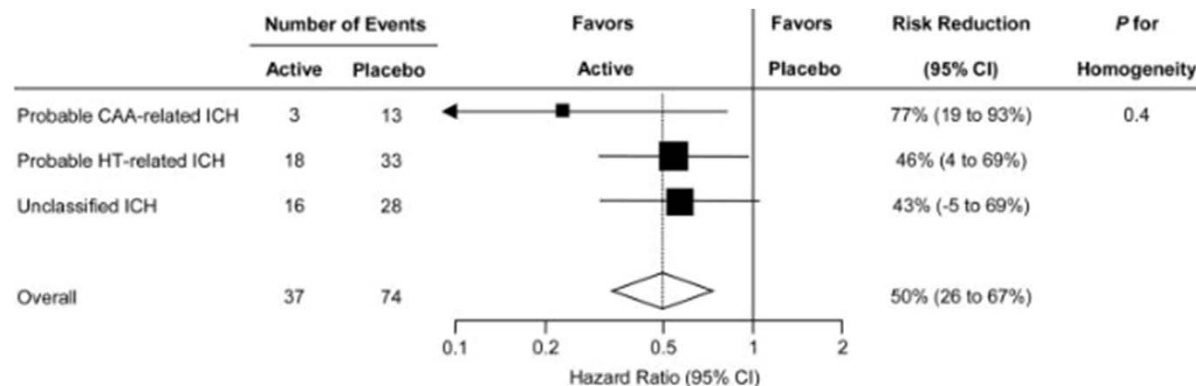- There was no difference in the magnitude of the effects of treatment among different types of ICH

	Number of Events		Favors Active	Favors Placebo	Risk Reduction (95% CI)	P for Homogeneity
	Active	Placebo				
Probable CAA-related ICH	3	13			77% (19 to 93%)	0.4
Probable HT-related ICH	18	33			46% (4 to 69%)	
Unclassified ICH	16	28			43% (-5 to 69%)	
Overall	37	74			50% (26 to 67%)	

Hazard Ratio (95% CI)   0.1   0.2   0.5   1   2

Figure. Effects of randomized treatment on the risks of different types of ICH. Solid boxes indicate estimates of treatment effect on the risks of ICH types; horizontal lines, 95% CI; diamond, the estimate and 95% CI for overall effect. Areas of the boxes are proportional to the event number.

What is the target BP?

AHA/ASA Guideline

Guidelines for the Management of Spontaneous Intracerebral Hemorrhage
A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.

Endorsed by the American Association of Neurological Surgeons, the Congress of Neurological Surgeons, and the Neurocritical Care Society

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BP should be controlled in all ICH patients (*Class I; Level of Evidence A*). (Revised from the previous guideline) **Measures to control BP should begin immediately after ICH onset (*Class I; Level of Evidence A*). (New recommendation) A long-term goal of BP <130 mmHg systolic and 80 mmHg diastolic is reasonable (*Class IIa; Level of Evidence B*). (New recommendation)**
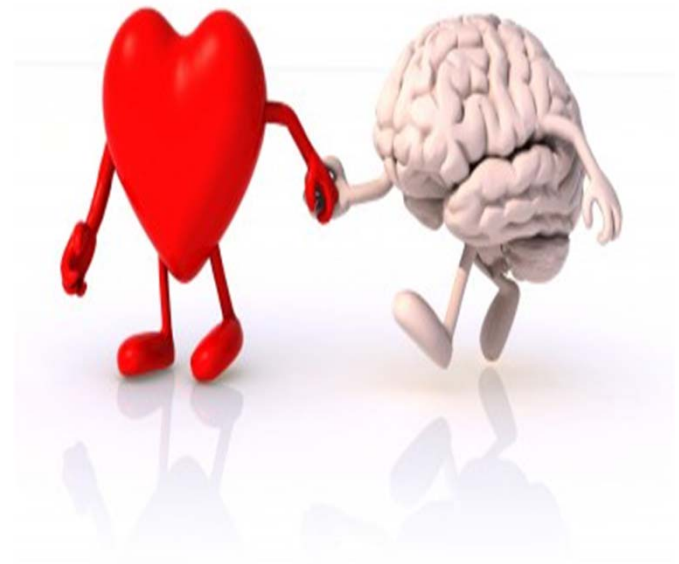
Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial

*The SPS3 Study Group**

Summary

Background Lowering of blood pressure prevents stroke but optimum target levels to prevent recurrent stroke are unknown. We investigated the effects of different blood-pressure targets on the rate of recurrent stroke in patients with recent lacunar stroke.

Methods In this randomised open-label trial, eligible patients lived in North America, Latin America, and Spain and had recent, MRI-defined symptomatic lacunar infarctions. Patients were recruited between March, 2003, and April, 2011, and randomly assigned, according to a two-by-two multifactorial design, to a systolic-blood-pressure target of 130–149 mm Hg or less than 130 mm Hg. The primary endpoint was reduction in all stroke (including ischaemic strokes and intracranial haemorrhages). Analysis was done by intention to treat. This study is registered with ClinicalTrials.gov, number NCT 00059306.

Findings 3020 enrolled patients, 1519 in the higher-target group and 1501 in the lower-target group, were followed up for a mean of 3·7 (SD 2·0) years. Mean age was 63 (SD 11) years. After 1 year, mean systolic blood pressure was 138 mm Hg (95% CI 137–139) in the higher-target group and 127 mm Hg (95% CI 126–128) in the lower-target group. Non-significant rate reductions were seen for all stroke (hazard ratio 0·81, 95% CI 0·64–1·03, p=0·08), disabling or fatal stroke (0·81, 0·53–1·23, p=0·32), and the composite outcome of myocardial infarction or vascular death (0·84, 0·68–1·04, p=0·32) with the lower target. The rate of intracerebral haemorrhage was reduced significantly (0·37, 0·15–0·95, p=0·03). Treatment-related serious adverse events were infrequent.

Interpretation Although the reduction in stroke was not significant, our results support that in patients with recent lacunar stroke, the use of a systolic-blood-pressure target of less than 130 mm Hg is likely to be beneficial.

SBP 130-149   SBP <130

	Higher-target group (n=1519)		Lower-target group (n=1501)		Hazard ratio (95% CI)	p value
	Number of patients	Rate (% per patient-year)	Number of patients	Rate (% per patient-year)		
Stroke						
All stroke	152	2·77%	125	2·25%	0·81 (0·64–1·03)	0·08
Ischaemic stroke or unknown	131	2·4%	112	2·0%	0·84 (0·66–1·09)	0·19
Intracranial haemorrhage						
All	21*	0·38%	13†	0·23%	0·61 (0·31–1·22)	0·16
Intracerebral	16	0·29%	6	0·11%	0·37 (0·15–0·95)	0·03
Subdural or epidural	5	0·091%	6	0·11%	1·18 (0·36–3·88)	0·78
Other	2	0·036%	4	0·072%	1·97 (0·36–10·74)	0·43
Disabling or fatal stroke‡	49	0·89%	40	0·72%	0·81 (0·53–1·23)	0·32
Myocardial infarction	40	0·70%	36	0·62%	0·88 (0·56–1·39)	0·59
Major vascular event*	188	3·46%	160	2·91%	0·84 (0·68–1·04)	0·10
Deaths						
All	101	1·74%	106	1·80%	1·03 (0·79–1·35)	0·82
Vascular death	41	0·70%	36	0·61%	0·86 (0·55–1·35)	0·52
Non-vascular	35	0·60%	40	0·68%	1·12 (0·71–1·76)	0·62
Uncertain	25	0·43%	30	0·51%	1·18 (0·69–2·00)	0·55

*One classified as both intracerebral and other, and one as both intracerebral and subdural or epidural. †One classified as intracerebral and subdural or epidural, and two as both intracerebral and other. ‡Disabling strokes classified as modified Rankin score 3 or higher after 3–6 months.

Table 2: Primary and secondary outcomes

Achieved BP and Outcomes in SPS3

- Post-hoc examination of the association of mean achieved BP 6 months after randomization with recurrent stroke, major vascular events, and all-cause mortality

- Mean follow up = 3.7 years

Odden et al. Hypertension. 2016;67:63-69.

- J-shaped relationship between BP & outcomes

- BP >124/67 mm Hg was associated with increased mortality (adjusted HR 1.9; 95% CI 1.4-2.7 for SBP and 2.2; 95% CI 1.4-3.6 for DBP)

- Below this level, this relationship was inverted (HR 0.29;95% CI 0.10-0.79 for SBP and 0.34; 95% CI 0.13- 0.89 for DBP)

- The lowest risk of all events occurred at SBP of ~ 120-128 mm Hg and DBP of ~ 65-70 mm Hg

Lower target blood pressures are safe and effective for the prevention of recurrent stroke: the PROGRESS trial

Hisatomi Arima[a], John Chalmers[a], Mark Woodward[a], Craig Anderson[a], Anthony Rodgers[b], Stephen Davis[c], Stephen MacMahon[a], Bruce Neal[a] for the PROGRESS Collaborative Group

Objective To explore the likely optimum blood pressure (BP) level for patients with a history of cerebrovascular disease.

Methods The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) was a randomized, placebo-controlled trial that established the beneficial effects of BP lowering in 6105 patients with cerebrovascular disease. The present study comprises two series of post hoc analyses. The first was designed to investigate the effects of randomized treatment on recurrent stroke by baseline BP levels, and the second was a corresponding observational analysis investigating the association between achieved follow-up BP levels and recurrent stroke risk.

Results Analyses of the randomized treatment comparisons showed that BP lowering with combination therapy produced similar risk reductions in each of four subgroups defined by baseline BP of less than 120, 120–139, 140–159, and 160 mmHg or greater (P homogeneity = 0.5). The effects of single-drug therapy were also comparable across these subgroups (P homogeneity = 0.2), but consistently greater benefits were observed with combination compared to single-drug therapy. The analyses of achieved follow-up BP showed that the lowest risk of recurrence was among the one-quarter of participants with the lowest follow-up BP levels (median 112/72 mmHg), and that risks rose progressively with higher follow-up BP levels. Minor side-effects were progressively more common at lower BP levels (P homogeneity = 0.04), but there was no excess of serious complications (all P homogeneity > 0.2).

Conclusion These analyses provide no evidence of a J-curve relationship between BP level and stroke risk among patients with cerebrovascular disease, and identify no patient group among whom more intensive BP lowering would not be expected to produce greater risk reductions. J Hypertens 24:1201–1208 © 2006 Lippincott Williams & Wilkins.

- The beneficial effects of treatment in preventing ICH extend down to patients with baseline BP levels ~ 115/ 75mmHg

- Progressive lowering BP to 115/75 mmHg in ICH patients over time was safe in PROGRESS

SBP (mmHg)	Events/patients Active	Placebo	Favours active	Favours placebo	Risk reduction (95% CI)	P trend
Ischaemic stroke						
≥160	48/524	84/543			43 (19 to 60)	0.4
140 to 159	47/695	65/689			30 (−2 to 52)	
120 to 139	30/486	39/461			28 (−16 to 55)	
<120	1/65	3/81			57 (−314 to 96)	
Total	126/1770	191/1774			36 (19 to 49)	
Haemorrhagic stroke						
≥160	5/524	17/543			70 (19 to 89)	0.09
140 to 159	2/695	17/689			88 (50 to 97)	
120 to 139	5/486	15/461			69 (15 to 89)	
<120	0/65	0/81			Not calculable	
Total	12/1770	49/1774			76 (55 to 87)	

Hazard ratio (95% CI)

o The association of stroke recurrence with achieved follow-up SBP level was strong and continuous in the range of achieved follow-up SBP from 112 to 168 mmHg

o This association remained strong even after controlling for the effects of other cardiovascular risk factors and of randomized treatment, and was not altered after adjustment for baseline BP

o Similar associations were observed for both IS & ICH although the relationship of ICH with achieved follow-up SBP level was stronger

Fig. 4
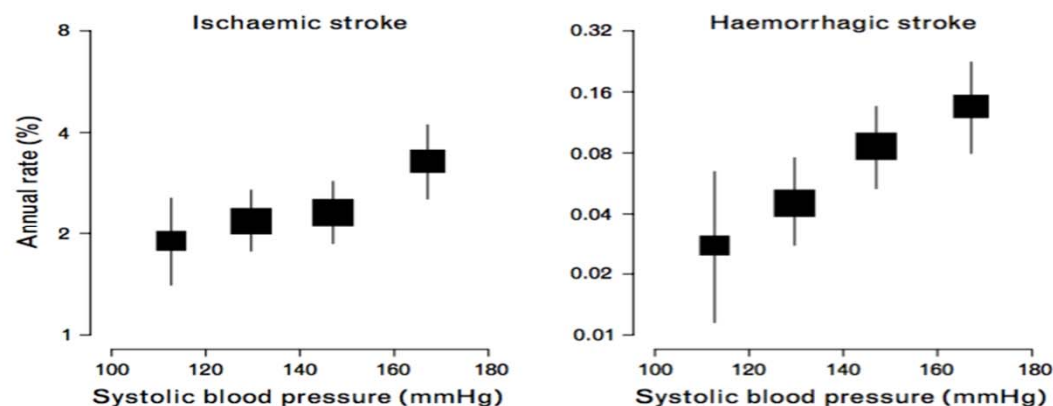
Annual rates of ischaemic and haemorrhagic stroke according to achieved follow-up systolic blood pressure levels. Conventions as for Fig. 3. *P* trend for ischaemic stroke = 0.0005, for haemorrhagic stroke < 0.0001. *P* homogeneity = 0.003.

Targeting SBP <120 mm Hg could be beneficial…

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*

ABSTRACT

BACKGROUND
The most appropriate targets for systolic blood pressure to reduce cardiovascular morbidity and mortality among persons without diabetes remain uncertain.

METHODS
We randomly assigned 9361 persons with a systolic blood pressure of 130 mm Hg or higher and an increased cardiovascular risk, but without diabetes, to a systolic blood-pressure target of less than 120 mm Hg (intensive treatment) or a target of less than 140 mm Hg (standard treatment). The primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes.

RESULTS
At 1 year, the mean systolic blood pressure was 121.4 mm Hg in the intensive-treatment group and 136.2 mm Hg in the standard-treatment group. The intervention was stopped early after a median follow-up of 3.26 years owing to a significantly lower rate of the primary composite outcome in the intensive-treatment group than in the standard-treatment group (1.65% per year vs. 2.19% per year; hazard ratio with intensive treatment, 0.75; 95% confidence interval [CI], 0.64 to 0.89; P<0.001). All-cause mortality was also significantly lower in the intensive-treatment group (hazard ratio, 0.73; 95% CI, 0.60 to 0.90; P=0.003). Rates of serious adverse events of hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure, but not of injurious falls, were higher in the intensive-treatment group than in the standard-treatment group.

CONCLUSIONS
Among patients at high risk for cardiovascular events but without diabetes, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause, although significantly higher rates of some adverse events were observed in the intensive-treatment group. (Funded by the National Institutes of Health; ClinicalTrials.gov number, NCT01206062.)

The members of the writing committee (Jackson T. Wright, Jr., M.D., Ph.D., Jeff D. Williamson, M.D., M.H.S., Paul K. Whelton, M.D., Joni K. Snyder, R.N., B.S.N., M.A., Kaycee M. Sink, M.D., M.A.S., Michael V. Rocco, M.D., M.S.C.E., David M. Reboussin, Ph.D., Mahboob Rahman, M.D., Suzanne Oparil, M.D., Cora E. Lewis, M.D., M.S.P.H., Paul L. Kimmel, M.D., Karen C. Johnson, M.D., M.P.H., David C. Goff, Jr., M.D., Ph.D., Lawrence J. Fine, M.D., Dr.P.H., Jeffrey A. Cutler, M.D., M.P.H., William C. Cushman, M.D., Alfred K. Cheung, M.D., and Walter T. Ambrosius, Ph.D.) assume responsibility for the overall content and integrity of the article. The affiliations of the members of the writing group are listed in the Appendix. Address reprint requests to Dr. Wright at the Division of Nephrology and Hypertension, University Hospitals Case Medical Center, Case Western Reserve University, 1100 Euclid Ave. Cleveland, OH 44106-6053, or at jackson.wright@case.edu.

*A complete list of the members of the Systolic Blood Pressure Intervention Trial (SPRINT) Research Group is provided in the Supplementary Appendix, available at NEJM.org.

Table 2. Primary and Secondary Outcomes and Renal Outcomes.*

Outcome	Intensive Treatment		Standard Treatment		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	% per year	no. of patients (%)	% per year		
All participants	(N = 4678)		(N = 4683)			
Primary outcome†	243 (5.2)	1.65	319 (6.8)	2.19	0.75 (0.64–0.89)	<0.001
Secondary outcomes						
Myocardial infarction	97 (2.1)	0.65	116 (2.5)	0.78	0.83 (0.64–1.09)	0.19
Acute coronary syndrome	40 (0.9)	0.27	40 (0.9)	0.27	1.00 (0.64–1.55)	0.99
Stroke	62 (1.3)	0.41	70 (1.5)	0.47	0.89 (0.63–1.25)	0.50
Heart failure	62 (1.3)	0.41	100 (2.1)	0.67	0.62 (0.45–0.84)	0.002
Death from cardiovascular causes	37 (0.8)	0.25	65 (1.4)	0.43	0.57 (0.38–0.85)	0.005
Death from any cause	155 (3.3)	1.03	210 (4.5)	1.40	0.73 (0.60–0.90)	0.003
Primary outcome or death	332 (7.1)	2.25	423 (9.0)	2.90	0.78 (0.67–0.90)	<0.001

Patients with DM, Stroke & difficult-to-treat HTN were excluded from SPRINT!

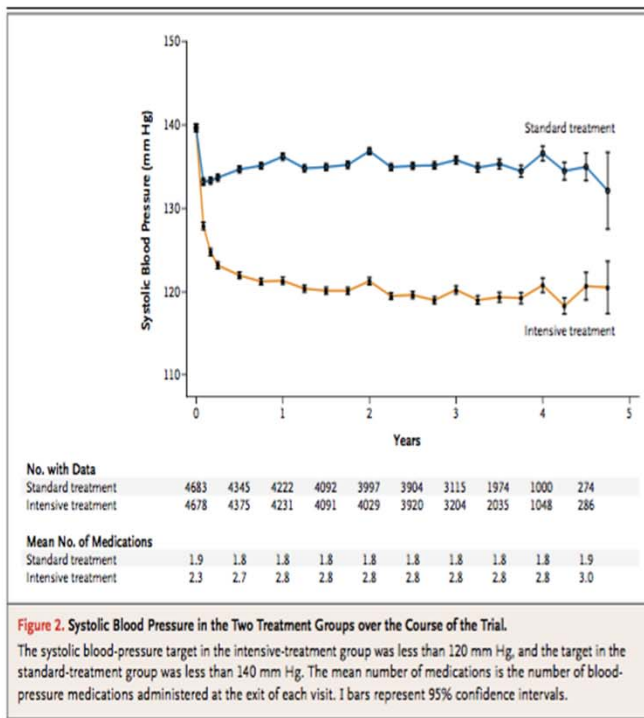○ Intensive lowering of BP requires >2 anti-HTN agents & comes with a price!

Figure 2. Systolic Blood Pressure in the Two Treatment Groups over the Course of the Trial.

The systolic blood-pressure target in the intensive-treatment group was less than 120 mm Hg, and the target in the standard-treatment group was less than 140 mm Hg. The mean number of medications is the number of blood-pressure medications administered at the exit of each visit. I bars represent 95% confidence intervals.

No. with Data

Standard treatment	4683	4345	4222	4092	3997	3904	3115	1974	1000	274
Intensive treatment	4678	4375	4231	4091	4029	3920	3204	2035	1048	286

Mean No. of Medications

Standard treatment	1.9	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.9
Intensive treatment	2.3	2.7	2.8	2.8	2.8	2.8	2.8	2.8	2.8	3.0

Table 3. Serious Adverse Events, Conditions of Interest, and Monitored Clinical Events.

Variable	Intensive Treatment (N = 4678)	Standard Treatment (N = 4683)	Hazard Ratio	P Value
	no. of patients (%)			
Serious adverse event*	1793 (38.3)	1736 (37.1)	1.04	0.25
Conditions of interest				
Serious adverse event only				
Hypotension	110 (2.4)	66 (1.4)	1.67	0.001
Syncope	107 (2.3)	80 (1.7)	1.33	0.05
Bradycardia	87 (1.9)	73 (1.6)	1.19	0.28
Electrolyte abnormality	144 (3.1)	107 (2.3)	1.35	0.02
Injurious fall†	105 (2.2)	110 (2.3)	0.95	0.71
Acute kidney injury or acute renal failure‡	193 (4.1)	117 (2.5)	1.66	<0.001
Emergency department visit or serious adverse event				
Hypotension	158 (3.4)	93 (2.0)	1.70	<0.001
Syncope	163 (3.5)	113 (2.4)	1.44	0.003
Bradycardia	104 (2.2)	83 (1.8)	1.25	0.13
Electrolyte abnormality	177 (3.8)	129 (2.8)	1.38	0.006
Injurious fall†	334 (7.1)	332 (7.1)	1.00	0.97
Acute kidney injury or acute renal failure‡	204 (4.4)	120 (2.6)	1.71	<0.001
Monitored clinical events				
Adverse laboratory measure§				
Serum sodium <130 mmol/liter	180 (3.8)	100 (2.1)	1.76	<0.001
Serum sodium >150 mmol/liter	6 (0.1)	0		0.02
Serum potassium <3.0 mmol/liter	114 (2.4)	74 (1.6)	1.50	0.006
Serum potassium >5.5 mmol/liter	176 (3.8)	171 (3.7)	1.00	0.97
Orthostatic hypotension¶				
Alone	777 (16.6)	857 (18.3)	0.88	0.01
With dizziness	62 (1.3)	71 (1.5)	0.85	0.35

My Thoughts..

○ ICH patients would likely have the lowest risk of ICH recurrence if their SBP could be lowered to ≤120-130 mmHg in the long term, provided that they can tolerate it

○ INTERACT-II suggests that this can be safely started within a few days after ICH…... ATTACH-II!!

○ How best to achieve & maintain greater BP reduction is challenging
  ○ Combination therapy might be preferable
  ○ Lifestyle modifications, and management of OSA and obesity are important
  ○ Improved support from health care providers & care takers, and patient education and involvement in BP monitoring are key to improve adherence to therapy

Use of antithrombotic agents

o A large number of ICH patients have cardiovascular comorbidities and are taking aspirin

o ~ 12% to 14% of ICH patients are taking an OAC at the time of ICH onset

o Survivors of ICH often have compelling indications for anticoagulant or antiplatelet medications

o OAC use is associated with increased mortality after ICH (up to 70%)

o The dilemma is whether to resume antithrombotic drugs or to discontinue them in ICH survivors lest they should raise the risk of recurrent ICH and/or worsen the outcome of any recurrence

Resumption of antithrombotic agents after ICH

o Should we?

o When?

o What agent?

o Under what circumstances?

  o Patient characteristics

  o ICH characteristics (location/etiology)

  ❖ No consensus

  ❖ No data from RCTs

  ❖ Various opinions based on a combination of observational data, small studies, pathophysiological considerations, and competing benefit/risk assessment

o Does aspirin increase the risk of ICH recurrence?

o If so, is there a preferential difference based on ICH location (lobar vs. non-lobar)?

Weimar et al, Cerebrovasc Dis. 2011;32:283-288.

Viswanathan et al, Neurology. 2006; 24;66:206-209.

- Prospective, observational
- 13 German centers
- 496 ICH patients; 141 (28.4%) received APL agents after ICH
- Mean follow up ~ 2 years

- Annual rate of ICH recurrence:
    - Non-lobar ICH = 2.9% (95% CI 1.6-4.1)
    - Lobar ICH = 7.2% (95% CI 3.8-10.6)

- No difference could be found for recurrent ICH under antiplatelet agents vs. no antithrombotic medication

- Prospective, observational
- Single center (USA)
- 207 ICH patients; 127 lobar & 80 non-lobar
- 27 lobar & 19 non-lobar ICH patients received APL agents after ICH
- Follow up ~ 2 years

- Cumulative 2-year ICH recurrence rate:
    - Lobar ICH = 22%
    - Non-lobar ICH = 4%

- APL use was not associated with ICH recurrence
    - HR 0.8, 95% CI 0.3-2.3) for lobar ICH
    - HR 1.2, 95% CI 0.1-14.3) for non-lobar ICH

- Prospective, observational
- Single center (Chinese)
- 440 ICH patients (predominantly non-lobar); 55 (12.7%) received ASA after ICH
- Follow up ~ 62.2±1.8 months

- 10.7% had recurrent ICH

- Patients prescribed aspirin did not have a higher risk of recurrent ICH compared with those not prescribed aspirin (22.7 per 1,000 patient-aspirin years vs. 22.4 per 1,000 patient years)

- In a subgroup analysis including 127 patients with indications for aspirin of whom 56 were prescribed aspirin
  - The incidence of combined vascular events including recurrent ICH, ischemic stroke, and acute coronary syndrome was lower in patients prescribed aspirin than those not prescribed aspirin (52.4 per 1,000 patient-aspirin years, vs. 112.8 per 1,000 patient-years, p=0.04)

Robert et al, Stroke. 2010;41:2606-2611.

- Observational
- Tayside, Scotland
- 417 ICH patients
  - 235 (56.4%) lobar
  - 139 (33.3%) non-lobar
  - 120 (28.7%) were prescribed APL agents
- Median follow-up ~ 36.5 months

- ICH recurrence:
  - Overall = 9.7 per 1000 patient-years (95% CI 5.3-16.4)
  - Non-lobar ICH = 6.4 per 1000 patient-years (95% CI 1.32-18.7)
  - Lobar ICH = 11.2 per 1000 patient-years (95% CI 5.1-21.3). All except one were lobar ICHs; 78% of recurrent ICHs occurred in patients not exposed to APLs.

- HR for recurrent ICH with APL use:
  - Overall = 1.07 (95% CI 0.24-4.84)
  - Lobar ICH = 1.52 (95% CI, 0.31–7.39)
  - Non-lobar ICH - No ICH events occurred among APL-treated patients

- APL use did not appear to have a clinically significant impact on the risk of recurrent ICH or subsequent IS/MI

Aspirin and recurrent intracerebral hemorrhage in cerebral amyloid angiopathy

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ABSTRACT

Objective: To identify and compare clinical and neuroimaging predictors of primary lobar intracerebral hemorrhage (ICH) recurrence, assessing their relative contributions to recurrent ICH.

Methods: Subjects were consecutive survivors of primary ICH drawn from a single-center prospective cohort study. Baseline clinical, imaging, and laboratory data were collected. Survivors were followed prospectively for recurrent ICH and intercurrent aspirin and warfarin use, including duration of exposure. Cox proportional hazards models were used to identify predictors of recurrence stratified by ICH location, with aspirin and warfarin exposures as time-dependent variables adjusting for potential confounders.

Results: A total of 104 primary lobar ICH survivors were enrolled. Recurrence of lobar ICH was associated with previous ICH before index event (hazard ratio [HR] 7.7, 95% confidence interval [CI] 1.4–15.7), number of lobar microbleeds (HR 2.93 with 2–4 microbleeds present, 95% CI 1.3–4.0; HR = 4.12 when ≥5 microbleeds present, 95% CI 1.6–9.3), and presence of CT-defined white matter hypodensity in the posterior region (HR 4.11, 95% CI 1.01–12.2). Although aspirin after ICH was not associated with lobar ICH recurrence in univariate analyses, in multivariate analyses adjusting for baseline clinical predictors, it independently increased the risk of ICH recurrence (HR 3.95, 95% CI 1.6–8.3, $p = 0.021$).

Conclusions: Recurrence of lobar ICH is associated with previous microbleeds or macrobleeds and posterior CT white matter hypodensity, which may be markers of severity for underlying cerebral amyloid angiopathy. Use of an antiplatelet agent following lobar ICH may also increase recurrence risk. **Neurology**® 2010;75:693–698

My Thoughts..

o Restarting/continuing aspirin in non-lobar ICH patients with indications for APL is reasonable

o In ICH patients with suspected CAA or microbleeds on MRI, the use of APLs should be:

  o Reserved for those with compelling indications, i.e. CAD, PVD, or AF

  o Restricted to the lowest dose (81 mg ASA), if possible

  o Perhaps avoided in those with recurrent lobar ICHs on APL therapy in whom BP is well controlled

○Does warfarin increase the risk of ICH recurrence?

○If so, is there a preferential difference based on ICH location (lobar vs. non-lobar)?

○ Any role for DOACs?

Poli et al. Neurology. 2014; 82:1020-1026

Yung et al, Can J Cardiol. 2012;28:33-39.

- The Cerebral Hemorrhage in patients Restarting Oral Anticoagulant Therapy (CHIRONE) Study
- Observational
- 267 patients affiliated with the Italian Federation of Anticoagulation Clinics who had received warfarin after ICH
- Mean follow up ~ 778 patient-years
- ICH recurred in 20 patients (7.5%; rate 2.56 × 100 patient-years) at a median time of 16.5 months, and was fatal in 5 patients (25%; rate 0.4 × 100 patient-years)
- Patients with a history of ICH carry a significant risk of recurrent ICH when treated with warfarin

- 284 consecutive patients with warfarin-related ICH admitted to 13 stroke centres in the Registry of the Canadian Stroke Network
- Warfarin was restarted in-hospital in 91 patients (32%)
- Mortality rates were not higher in those who restarted warfarin in-hospital: 31.9% vs. 54.4% (30-day, $P < 0.001$) and 48% vs. 61% (1-year, $P = 0.04$), and bleeding was not increased
- In selected patients at high risk for thromboembolism, reinitiation of warfarin after ICH did not confer increased mortality or bleeding events

Effect of Anticoagulation on Hospitalization Costs After Intracranial Hemorrhage in Atrial Fibrillation
A Registry Study

Anne Sig Vestergaard, MMsc; Flemming Skjøth, MSc, PhD; Gregory Y.H. Lip, MD;
Torben Bjerregaard Larsen, MD, PhD

Background and Purpose—Intracranial hemorrhage (ICH) is the most feared adverse event with oral anticoagulant therapy in patients with atrial fibrillation. The health economic aspects of resuming oral anticoagulant therapy after ICH are unknown. The aim was to estimate hospitalization costs of thromboembolism and hemorrhage subsequent to ICH in 2 patient groups with atrial fibrillation surviving the first 90 days post ICH: (1) patients resuming warfarin therapy within 90 days post ICH and (2) patients discontinuing therapy.

Methods—Retrospective data from Danish national registries were linked to identify patients with atrial fibrillation who suffered an ICH between January 1, 1997, and April 1, 2011. Study start was 90 days after incident ICH. Mortality was evaluated using the Kaplan–Meier estimate. Occurrence of hospitalization-requiring thromboembolism and hemorrhage was used to estimate hospitalization costs by linkage of *International Classification of Diseases*, Tenth Revision, codes to Danish Diagnosis–Related Group tariffs. The effect of resuming warfarin therapy on average 3-year hospitalization costs was estimated by regression analysis adjusted for between-group differences in baseline characteristics.

Results—In the inclusion period, 2162 patients had an ICH; 1098 survived the first 90 days and were included for analysis, and of those, 267 resumed warfarin therapy. Therapy resumption reduced the mean 3-year hospitalization cost of hospitalized patients significantly by US$ 1588 (95% confidence interval, −2925 to −251) and was significantly correlated with fewer hospitalization days per hospitalized patient (−4.6 [95% confidence interval, −7.6 to −1.6]). The marginal effect of therapy resumption on hospitalization costs per patient was US$ −407 (95% confidence interval, −815 to 2).

Conclusions—Resuming warfarin therapy within 90 days after ICH in patients with atrial fibrillation is associated with a decrease in average hospitalization costs.   (*Stroke*. 2016;47:979-985. DOI: 10.1161/STROKEAHA.115.012338.)

Supplemental Table III. Crude incidence rate of events in the resumption and discontinuation group and crude and adjusted hazard ratios of composite outcomes of the resumption group versus the discontinuation group based on three years of follow-up after the index date*

Outcome	OAC resumption group (n=267)		OAC discontinuation group (n=831)		Crude hazard ratio	Adjusted Hazard ratio‡
	Crude incidence, n	Incidence rate†, 95% CI	Crude incidence (n)	Incidence rate†, 95% CI	Mean, 95% CI	Mean, 95% CI
All-cause mortality	80	11.76 [9.44;14.64]	316	16.26 [14.56;18.15]	0.73 [0.57;0.93]	0.79 [0.61;1.01]
Ischemic stroke	17	2.57 [1.60;4.14]	88	4.82 [3.91;5.94]	0.69 [0.45;1.08]	0.77 [0.49;1.19]
Transient ischemic attack	9	1.34 [0.70;1.49]	18	0.94 [0.59;1.49]		
Myocardial infarction	5	0.74 [0.31;1.77]	18	0.93 [0.59;1.48]	0.63 [0.32;1.24]	0.65 [0.32;1.30]
PE, SE, DVT§	5	0.74 [0.31;1.78]	28	1.46 [1.01;2.11]		
Intracranial hemorrhage	10	1.48 [0.80;2.75]	32	1.69 [1.19;2.38]	0.90 [0.44;1.83]	0.90 [0.44;1.85]
Major extracranial hemorrhage	9	1.34 [0.70;2.58]	13	0.67 [0.39;1.16]	1.32 [0.65;2.69]	1.34 [0.65;2.75]
Gastrointestinal hemorrhage	2	0.29 [0.07;1.17]	11	0.57 [0.32;1.03)		

Resumption of warfarin →
o Correlated with fewer hospitalization days per patient
o Reduced 3-year hospitalization costs

cHR: 0.73 [95% CI: 0.37;0.93]
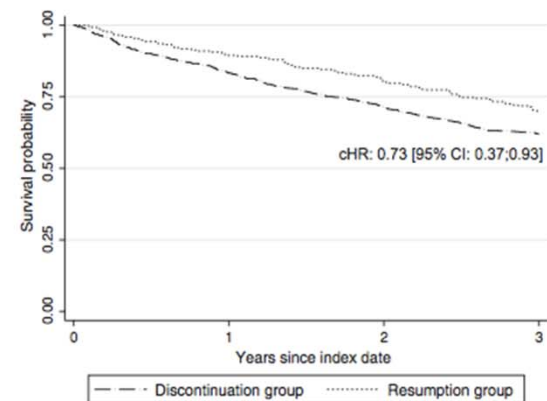
Figure 3. Kaplan–Meier curve of 3-year survival after index date. cHR indicates crude hazard ratio; and CI, confidence interval.

Can Patients Be Anticoagulated After Intracerebral Hemorrhage?
A Decision Analysis

Mark H. Eckman, MD; Jonathan Rosand, MD; Katherine A. Knudsen, BA;
Daniel E. Singer, MD; Steven M. Greenberg, MD, PhD

Background and Purpose—Warfarin increases both the likelihood and the mortality of intracerebral hemorrhage (ICH), particularly in patients with a history of prior ICH. In light of this consideration, should a patient with both a history of ICH and a clear indication for anticoagulation such as nonvalvular atrial fibrillation be anticoagulated? In the absence of data from a clinical trial, we used a decision-analysis model to compare the expected values of 2 treatment strategies—warfarin and no anticoagulation—for such patients.

Methods—We used a Markov state transition decision model stratified by location of hemorrhage (lobar or deep hemispheric). Effectiveness was measured in quality-adjusted life years (QALYs). Data sources included English language literature identified through MEDLINE searches and bibliographies from selected articles, along with empirical data from our own institution. The base case focused on a 69-year-old man with a history of ICH and newly diagnosed nonvalvular atrial fibrillation.

Results—For patients with prior lobar ICH, withholding anticoagulation therapy was strongly preferred, improving quality-adjusted life expectancy by 1.9 QALYs. For patients with prior deep hemispheric ICH, withholding anticoagulation resulted in a smaller gain of 0.3 QALYs. In sensitivity analyses for patients with deep ICH, anticoagulation could be preferred if the risk of thromboembolic stroke is particularly high.

Conclusions—Survivors of lobar ICH with atrial fibrillation should not be offered long-term anticoagulation. Similarly, most patients with deep hemispheric ICH and atrial fibrillation should not receive anticoagulant therapy. However, patients with deep hemispheric ICH at particularly high risk for thromboembolic stroke or low risk of ICH recurrence might benefit from long-term anticoagulation. (*Stroke*. 2003;34:1710-1716.)

Key Words: atrial fibrillation ■ decision support techniques ■ intracerebral hemorrhage
■ Markov chains ■ warfarin

- Lobar ICH – Do not anticoagulate UNLESS the rate of recurrent ICH is <1.4% per year
- Non-lobar ICH -- Do not anticoagulate UNLESS the rate of recurrent ICH is <1.6% per year & the rate of ischemic stroke is >7% per year (CHADS2≥ 4 or CHA2DS2-VASc ≥ 5)
- All survivors of lobar ICH & most survivors of non-lobar ICH should not be anticoagulated

Balancing the risks…

- ICH results in greater disability & mortality than ischemic stroke.
- Restarting anticoagulation should be avoided, UNLESS the risk of ischemic stroke is MUCH HIGHER than that of recurrent ICH
- The risk of thromboembolic events depends on the underlying indication for OAC and comorbidities
- The risk for ICH recurrence depends on ICH subtype/location
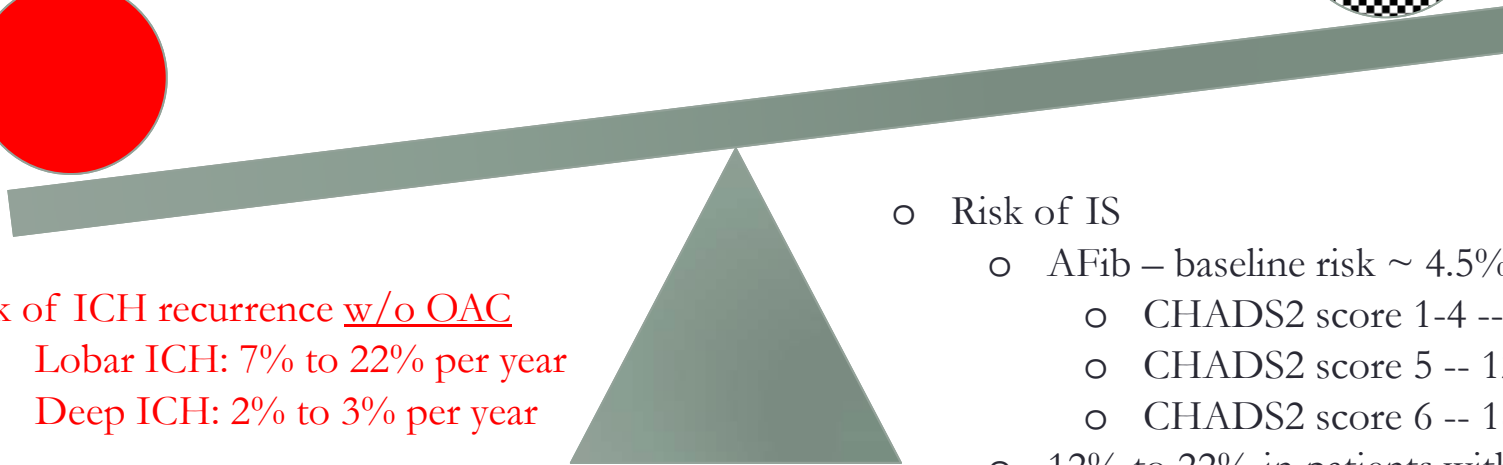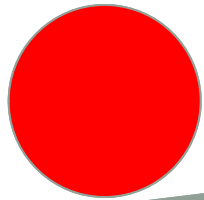
- Risk of ICH recurrence w/o OAC
  - Lobar ICH: 7% to 22% per year
  - Deep ICH: 2% to 3% per year

Most anticoagulation-related ICHs are lobar

- Risk of IS
  - AFib – baseline risk ~ 4.5% per year
    - CHADS2 score 1-4 -- 2.8%- 8.5%
    - CHADS2 score 5 -- 12.5%
    - CHADS2 score 6 -- 18%
  - 12% to 22% in patients with prosthetic valves

Optimal Timing of Resumption of Warfarin After Intracranial Hemorrhage

Ammar Majeed, MD; Yang-Ki Kim, MD; Robin S. Roberts, PhD;
Margareta Holmström, MD, PhD; Sam Schulman, MD, PhD

Background and Purpose—The optimum timing of resumption of anticoagulation after warfarin-related intracranial hemorrhage in patients with indication for continued anticoagulation is uncertain. We performed a large retrospective cohort study to obtain more precise risk estimates.

Methods—We reviewed charts of 2869 consecutive patients with objectively verified intracranial hemorrhage over 6 years at 3 tertiary centers. We calculated the daily risk of intracranial hemorrhage or ischemic stroke with and without resumption of warfarin; we focused on patients who survived the first week and had cardiac indication for anticoagulation or previous stroke. Using a Cox model, we estimated rates for these 2 adverse events in relation to different time points of resumed anticoagulation. The combined risk of either a new intracranial hemorrhage or an ischemic stroke was calculated for a range of warfarin resumption times.

Results—We identified warfarin-associated intracranial hemorrhage in 234 patients (8.2%), of whom 177 patients (76%) survived the first week and had follow-up information available; the median follow-up time was 69 weeks (interquartile range [IQR] 19–144). Fifty-nine patients resumed warfarin after a median of 5.6 weeks (IQR 2.6–17). The hazard ratio for recurrent intracranial hemorrhage with resumption of warfarin was 5.6 (95% CI, 1.8–17.2), and for ischemic stroke it was 0.11 (95% CI, 0.014–0.89). The combined risk of recurrent intracranial hemorrhage or ischemic stroke reached a nadir if warfarin was resumed after approximately 10 to 30 weeks.

Conclusion—The optimal timing for resumption of warfarin therapy appears to be between 10 and 30 weeks after warfarin-related intracranial hemorrhage. (*Stroke*. 2010;41:2860-2866.)

Key Words: intracranial hemorrhage ■ anticoagulation ■ ischemic stroke ■ management

Table 3. Cox Proportional Hazards Model for Recurrent Intracranial Hemorrhage or for Ischemic Event at Different Time Intervals With and Without Resumption of Warfarin

Warfarin Status	Risk of Intracranial Hemorrhage per Day				Risk of Ischemic Stroke per Day		
	1–35 Days	36–63 Days	64–217 Days	≥218 Days	1–77 Days	78–329 Days	≥330 Days
Observed rate n (%)							
No	7/3829 (0.18%)	1/2250 (0.044%)	0/10146 (0.00%)	0/32208 (0.00%)	5/7301 (0.068%)	6/15360 (0.039%)	4/24112 (0.017%)
Yes	2/265 (0.75%)	1/504 (0.20%)	2/4008 (0.049%)	2/29056 (0.0069%)	0/1152 (0.00%)	0/6830 (0.00%)	1/28325 (0.0035%)
Hazard ratio	4.13	4.46	∞	∞	0.00	0.00	0.21
Rate used in prediction model*							
No	0.18%	0.044%	0.0090%†	0.0012%†	0.068%	0.039%	0.017%
Yes	1.02%‡	0.25%‡	0.049%	0.0069%	0.0075%§	0.0043%§	0.0018%§

*The Cox proportional hazard model provided a Warfarin Hazard Ratio for recurrent intracranial hemorrhage of 5.57 (95% CI, 1.80–17.25; $P=0.0029$) and for ischemic stroke of 0.11 (95% CI, 0.0139–0.868; $P=0.036$). The rates used in the prediction model were based on the following hazard ratios:
†Observed rate on warfarin/5.57.
‡Observed rate without warfarin×5.57.
§Observed rate without warfarin ×0.11. The remaining proposed rates are those actually observed.

Figure 2. The "total" risk for a treatment horizon of 3 years of recurrent intracranial hemorrhage and of ischemic stroke according to the time point of resumption of anticoagulation.
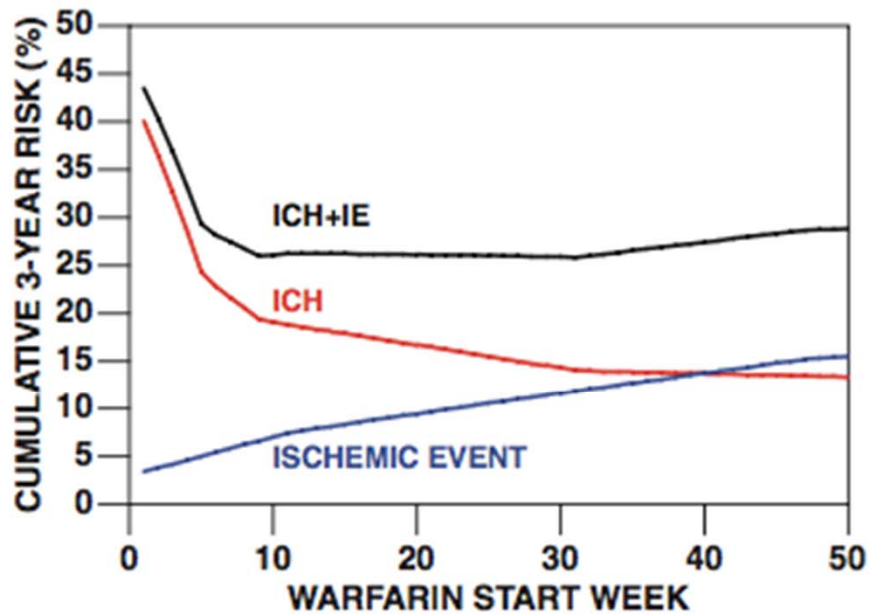
Time of Resumption of OAC	Rate of recurrent ICH	Rate of TTE
Within 2 weeks	36%	4%
Within 5 weeks	24%	5%
Within 10 weeks	19%	7%

Pennlert et al, ESOC, Barcelona, 2016

o Swedish nationwide observational study of 2619 patients w/ AF who survived their first-ever ICH during the period from 2005-2012

o Cumulative incidence of IS, MI, systemic embolism, ICH, other fatal hemorrhagic event, or death of other cause within a 3-year follow-up period

o When OAC was started within 8-12 weeks after ICH, the incidence of an event (18% vs. 27.5%; 95% CI 4.5-14.3)

o Starting OAC before week 8 increased the incidence of severe bleeding (albeit non-significant)

o AC reduces the total risk of an event both in low- and high-risk ICH patients w/ AF

o The optimal timing of initiating AC is 8-12 weeks following ICH

o LAA closure

o Antiplatelet therapy

o NOACS/DOACS

DOACS?

Apixaban in Patients with Atrial Fibrillation

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ABSTRACT

BACKGROUND

Vitamin K antagonists have been shown to prevent stroke in patients with atrial fibrillation. However, many patients are not suitable candidates for or are unwilling to receive vitamin K antagonist therapy, and these patients have a high risk of stroke. Apixaban, a novel factor Xa inhibitor, may be an alternative treatment for such patients.

METHODS

In a double-blind study, we randomly assigned 5599 patients with atrial fibrillation who were at increased risk for stroke and for whom vitamin K antagonist therapy was unsuitable to receive apixaban (at a dose of 5 mg twice daily) or aspirin (81 to 324 mg per day), to determine whether apixaban was superior. The mean follow-up period was 1.1 years. The primary outcome was the occurrence of stroke or systemic embolism.

RESULTS

Before enrollment, 40% of the patients had used a vitamin K antagonist. The data and safety monitoring board recommended early termination of the study because of a clear benefit in favor of apixaban. There were 51 primary outcome events (1.6% per year) among patients assigned to apixaban and 113 (3.7% per year) among those assigned to aspirin (hazard ratio with apixaban, 0.45; 95% confidence interval [CI], 0.32 to 0.62; P<0.001). The rates of death were 3.5% per year in the apixaban group and 4.4% per year in the aspirin group (hazard ratio, 0.79; 95% CI, 0.62 to 1.02; P=0.07). There were 44 cases of major bleeding (1.4% per year) in the apixaban group and 39 (1.2% per year) in the aspirin group (hazard ratio with apixaban, 1.13; 95% CI, 0.74 to 1.75; P=0.57); there were 11 cases of intracranial bleeding with apixaban and 13 with aspirin. The risk of a first hospitalization for cardiovascular causes was reduced with apixaban as compared with aspirin (12.6% per year vs. 15.9% per year, P<0.001). The treatment effects were consistent among important subgroups.

CONCLUSIONS

In patients with atrial fibrillation for whom vitamin K antagonist therapy was un-

Table 3. Rates of Study Outcomes in the Two Treatment Groups.

Outcome	Apixaban (N=2808) no. of patients with first event	%/yr	Aspirin (N=2791) no. of patients with first event	%/yr	Hazard Ratio with Apixaban (95% CI)	P Value
Stroke or systemic embolism	51	1.6	113	3.7	0.45 (0.32–0.62)	<0.001
Stroke, systemic embolism, or death	143	4.6	223	7.2	0.64 (0.51–0.78)	<0.001
Stroke, systemic embolism, myocardial infarction or death from vascular cause	132	4.2	197	6.4	0.66 (0.53–0.83)	<0.001
Stroke, systemic embolism, myocardial infarction, death from vascular cause, or major bleeding event	163	5.3	220	7.2	0.74 (0.60–0.90)	0.003
Stroke†	49	1.6	105	3.4	0.46 (0.33–0.65)	<0.001
Ischemic	35	1.1	93	3.0	0.37 (0.25–0.55)	<0.001
Hemorrhagic	6	0.2	9	0.3	0.67 (0.24–1.88)	0.45
Unspecified	9	0.3	4	0.1	2.24 (0.69–7.27)	0.18
Disabling or fatal	31	1.0	72	2.3	0.43 (0.28–0.65)	<0.001
Systemic embolism	2	0.1	13	0.4	0.15 (0.03–0.68)	0.01
Myocardial infarction	24	0.8	28	0.9	0.86 (0.50–1.48)	0.59
Death						
From any cause	111	3.5	140	4.4	0.79 (0.62–1.02)	0.07
From vascular cause	84	2.7	96	3.1	0.87 (0.65–1.17)	0.37
Hospitalization for cardiovascular cause	367	12.6	455	15.9	0.79 (0.69–0.91)	<0.001
Bleeding event						
Major	44	1.4	39	1.2	1.13 (0.74–1.75)	0.57
Intracranial	11	0.4	13	0.4	0.85 (0.38–1.90)	0.69
Subdural‡	4	0.1	2	0.1	—	—
Other intracranial, excluding hemorrhagic stroke and subdural‡	1	<0.1	2	0.1	—	—
Extracranial or unclassified	33	1.1	27	0.9	1.23 (0.74–2.05)	0.42
Gastrointestinal	12	0.4	14	0.4	0.86 (0.40–1.86)	0.71
Non-gastrointestinal	20	0.6	13	0.4	1.55 (0.77–3.12)	0.22
Fatal§	4	0.1	6	0.2	0.67 (0.19–2.37)	0.53
Clinically relevant nonmajor	96	3.1	84	2.7	1.15 (0.86–1.54)	0.35
Minor	188	6.3	153	5.0	1.24 (1.00–1.53)	0.05

Several trials are being planned

Fahmy et al, Can J Cardiol. 2016 ;32:349-354

Johnsen et al, 2nd ESOC, Barcelona, 2016

o 24 patients with previous ICH underwent LAAO

o Mean CHADS2 score = 3.2 ± 1.4

o Mean follow-up = 11.9 ± 13.3 months

o 1 patient died (unrelated to device) and 1 patient had a TIA

o No ischemic or hemorrhagic strokes occurred during follow-up

• Compared outcomes of 147 patients w/ AF & ICH from Nordic countries who underwent LAAO from 2009-1015 to propensity score (HAS-BLED & CHA2DS2-VASc) matched group of 147 Danish patients receiving standard therapy (warfarin 20%; NOACs 23%; APL 37%)

• LAAO group had lower risk of the composite endpoint, ischemic stroke, major bleeding, and all-cause mortality; HR 0.19 (95% CI 0.08-0.46); RRR 81%

• RRR for ICH = 71%; IS = 65%; major bleeding 61%; and mortality 92%

• Phase III (STROKECLOSE) is about to start in Nordic countries

My Thoughts

o In most AF patients with warfarin-associated lobar ICH & suspected CAA, the risk for warfarin-related ICH recurrence seems higher than thromboembolic events and, therefore would be best managed without resumption of warfarin therapy.

o In the subset of patients with lobar ICH at high baseline risk for ischemic stroke (e.g. CHADS2 ≥5), LAA closure (Watchman LAA occlusion device) is a viable option. If LAA is not feasible and OAC is considered, the use of DOACS (e.g. Apixaban) might be an alternative to warfarin.

o In most AF patients with warfarin-related non-lobar (deep) ICH, the risk of warfarin-related ICH recurrence seems equivalent to or lower than the risk of thromboembolic events. Therefore, they may receive net benefit from resumption of OAC. LAA closure or apixaban are reasonable alternatives to warfarin.

o In warfarin-related ICH patients with prosthetic valves, the risk of thromboembolic events is higher than the risk of recurrent ICH (regardless of ICH location). In these patients, resumption of OAC with warfarin is often required. *Please note that DOACS are contraindicated in patients with prosthetic valves!*

o The optimal time to resumption of anticoagulation after warfarin-related ICH is unclear and may vary from patient to patient. Avoidance of OAC for 4-8 weeks, in patients without mechanical heart valves, might decrease the risk of ICH recurrence.

Use of Statins

Number of prescriptions of statins is rapidly rising ~ by 500,000 a month!

Number of people taking atorvastatin alone increased from 25 to 56 million after the recent ACC/AHA 2013 lipid management guidelines!

"We found a bunch of these clogging your arteries. They're cholesterol pills."

Resumption of statins after ICH

o Should we?

o When?

o What agent?

o Under what circumstances?

  o Patient characteristics
  o ICH characteristics (location/etiology)

  ❖ No consensus
  ❖ No data from RCTs
  ❖ Various opinions based on a combination of observational data, small studies, pathophysiological considerations, and competing benefit/risk assessment

Balancing the risks…

o   Decreased risk of MACCE

o   Pleotropic effects leading to enhancement of recovery

o   Increased risk of ICH recurrence

o   Concern about increased risk of cognitive decline from accumulating microbleeds

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812   AUGUST 10, 2006   VOL. 355 NO. 6
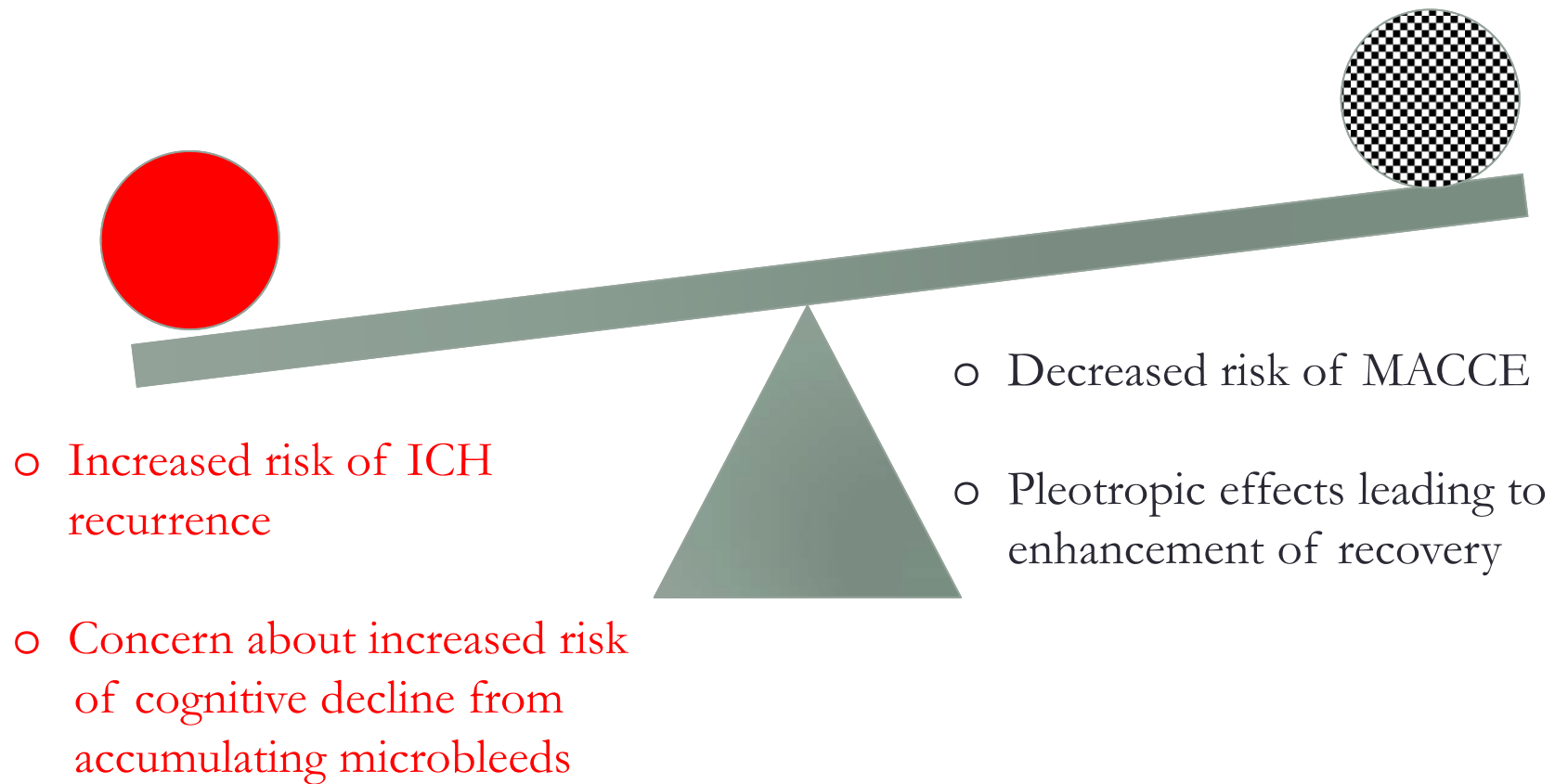
High-Dose Atorvastatin after Stroke or Transient Ischemic Attack

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators*

- Overall incidence of ICH was 1.8%, BUT
  - ICH was significantly higher in the atorvastatin group vs. the placebo group (2.3% vs. 1.4%)
  - Relative risk of ICH on statin = 1.68 (95% CI: 1.09-2.59), compared with placebo
  - Statins treatment, increasing age, male sex, and having ICH as the qualifying stroke to be enrolled in the study were associated with increased risk for ICH

- 93 out of 4,731 (2%) of subjects enrolled in SPARCL had ICH as the index event (45 received atorvastatin and 48 placebo). These patients did not seem to benefit from atorvastatin:
  - Stroke or TIA occurred in 14.6% of placebo-treated patients vs. 24.4% of atorvastatin-treated patients
  - Major cardiovascular events occurred in 12.5% vs. 24.4%; and death in 10.4% vs. 15.6%

- The risk for ICH was independent of the effects of statin therapy cholesterol levels

Should Statins be Avoided after Intracerebral Hemorrhage?

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Abstract

Context—Statins are widely prescribed for primary and secondary prevention of ischemic cardiac and cerebrovascular disease. Although serious adverse effects are uncommon, results from a recent clinical trial suggested increased risk of intracerebral hemorrhage (ICH) associated with statin use. For patients with baseline elevated risk of ICH, it is not known whether this potential adverse effect offsets the cardiovascular and cerebrovascular benefits.

Methods—We used Markov decision modeling to address the following clinical question: Given a history of prior ICH, should statin therapy be avoided? We investigated how a range of clinical parameters affects this decision, including hemorrhage location (deep vs lobar), ischemic cardiac and cerebrovascular risks, and magnitude of ICH risk associated with statins.

Findings—Avoiding statins was favored over a wide range of values for many clinical parameters, particularly in survivors of lobar ICH who are at highest risk of ICH recurrence. In survivors of lobar ICH without prior cardiovascular events, avoiding statins yielded a life expectancy gain of 2.2 quality-adjusted life years compared with statin use. This net benefit persisted even at the lower 95% confidence interval of the relative risk of statin-associated ICH. In lobar ICH patients with prior cardiovascular events, the annual recurrence risk of myocardial infarction would have to exceed 90% to favor statin therapy. Avoiding statin therapy was also favored, although by a smaller margin, in both primary and secondary prevention settings for survivors of deep ICH.

Conclusions—Avoiding statins should be considered for patients with a history of ICH, particularly those of lobar location.

- Statin use in survivors of lobar ICH increases the rate of ICH recurrence from 14% to 22% per year (relative risk increase of 1.57)

- This small increase in ICH risk was sufficient to offset any potential benefits for both primary and secondary cardiovascular prevention over a wide range of stipulated event rates

- In sensitivity analyses, avoiding statins remained the preferred option over a wide range of values for statins-associated relative risk for ICH, including the lower limit of the 95% CI of the relative risk for ICH reported in SPARCL, and stipulated MACCE rates

Statin Use and Microbleeds in Patients With Spontaneous Intracerebral Hemorrhage

Diogo C. Haussen, MD; Nils Henninger, MD; Sandeep Kumar, MD; Magdy Selim, MD, PhD

Background and Purpose—Statins have been associated with increased risk of intracerebral hemorrhage (ICH), particularly in elderly patients with previous ICH. Recurrent ICH in the elderly is often related to cerebral amyloid angiopathy. Therefore, we investigated whether statin use is associated with increased prevalence and severity of microbleeds (MB), particularly cortico-subcortical microbleeds (csMB), which are frequently observed in cerebral amyloid angiopathy.

Methods—We studied 163 consecutive patients with spontaneous ICH who underwent magnetic resonance imaging within 30 days of presentation. We retrieved clinical information and analyzed magnetic resonance imaging for the presence, location, and number of MB, which were divided into csMB or other (other MB). We performed group comparisons stratified by statin use and by the presence vs absence of any MB (csMB and/or other MB) or csMB alone.

Results—Sixty-four percent had lobar ICH. Overall, 53% had microbleeds and 39% had csMB. Statin users were older, had significantly lower cholesterol and low-density lipoprotein levels, and higher prevalence of hypertension, diabetes, dyslipidemia, and antiplatelet use. The prevalence and number of other MB were similar in statin-treated and statin-untreated individuals. However, more statin-treated patients had csMB (57% vs 33%; $P=0.007$), with almost twice as many lesions (4.6 ± 11.3 vs 2.4 ± 8.0; $P=0.007$) compared with untreated patients. Age and statin use were independently associated with both the presence and increased number of MB (odds ratio [OR], 1.03; 95% confidence interval [CI], 1.00–1.05; $P=0.01$ and OR, 2.72; 95% CI, 1.02–7.22; $P=0.04$, respectively) and csMB (OR, 1.03; 95% CI, 1.00–1.06; $P=0.01$ and OR, 4.15; 95% CI, 1.54–11.20; $P<0.01$) in multivariate analyses.

Conclusions—Statin use in patients with ICH is independently associated with MB, especially csMB. Future studies are needed to confirm our findings and to investigate whether csMB can serve as a surrogate marker for ICH risk in statin-treated patients. (*Stroke*. 2012;43:2677-2681.)

Table 4. Multivariate Logistic Regression Analysis for Presence of Cortico-Subcortical Microbleed

Variable	OR	95% CI	P
Age	1.03	1.00–1.06	0.012*
Male	0.66	0.33–1.31	0.240
Hypertension	0.91	0.42–1.94	0.812
Diabetes	0.42	0.15–1.14	0.090
Dyslipidemia	0.72	0.29–1.75	0.471
Coronary artery disease	0.97	0.35–2.69	0.965
Antiplatelet use	0.75	0.33–1.69	0.496
Statin use	4.15	1.54–11.20	0.005*

CI indicates confidence interval; OR, odds ratio.

Apolipoprotein E, Statins and Risk of Intracerebral Hemorrhage

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Abstract

Background and Purpose—*Apolipoprotein E (ApoE)* genotypes have been associated with lobar intracerebral hemorrhage (ICH). Although HMG-CoA reductase inhibitors (statins) have been associated with an increased risk of ICH, meta-analyses have not consistently shown a statin-induced risk of ICH. Here, we test whether hypercholesterolemia and *ApoE* polymorphisms affect the risk with ICH by statin use.

Methods—The Genetic and Environmental Risk Factors for Hemorrhagic Stroke study is a prospective, demographically-matched case-control study of ICH. A similar study of ICH, Genetic Risks for Medication-Related Hemorrhagic Stroke study, was used as a replication cohort. Subjects were classified as normocholesterolemia (NC), hypercholesterolemia without statin (HC-NS), and hypercholesterolemia with statin use (HC-S). Statistical comparisons were performed using Fisher's Exact Test, chi-square tests, and the Breslow-Day test.

Results—The discovery cohort consisted of 558 ICH cases and 1,444 controls, and the replication cohort consisted of 1,020 ICH cases and 382 controls. The association of lower risk for hypercholesterolemia was not attenuated by statin use. Statin use was observed to confer a higher risk for lobar ICH in those carrying *ApoE4/E4* and *ApoE2/E4* genotypes in both discovery and replication cohorts and combined, showed a trend towards significance (p=0.11 for Statin vs. *ApoE4/E4*).

Table 3. Risk of Lobar ICH by ApoE Carrier Status and Hypercholesterolemia vs No Hypercholesterolemia

	Discovery Sample				Replication Sample			
	Case	Control	OR (CI)	P Value	Case	Control	OR (CI)	P Value
ApoE2 carriers vs E3/E3								
Normocholesterolemia	33 (39%)	53 (24%)	2.06 (1.21–3.51)	0.01	86 (36%)	20 (17%)	2.87 (1.65–4.97)	0.0002
Hypercholesterolemia	28 (46%)	27 (18%)	3.93 (2.04–7.55)	<0.0001	24 (22%)	28 (16%)	1.69 (0.91–3.32)	0.09
ApoE4 carriers vs E3/E3								
Normocholesterolemia	42 (45%)	73 (30%)	1.90 (1.17–3.11)	0.01	112 (42%)	40 (29%)	1.82 (1.17–2.83)	0.008
Hypercholesterolemia	33 (50%)	73 (37%)	1.71 (0.98–3.00)	0.08	54 (39%)	49 (25%)	2.00 (1.25–3.21)	0.004

ApoE indicates apolipoprotein E; CI, confidence interval; ICH, intracerebral hemorrhage; and OR, odds ratio.

Pezzini et al. JNNP. 2016 (Epub)

- Compared 3492 consecutive patients having ICH with 3492 age and sex-matched stroke-free control subjects in a case-control analysis, as part of the Multicenter Study on Cerebral Hemorrhage in Italy (MUCH-Italy)

- There was an interaction between total serum cholesterol levels and statin use for the risk of ICH (IOR), 1.09; 95% CI 1.05- 1.12)

- Increasing levels of total serum cholesterol were associated with a decreased risk of ICH within statin strata (OR, 0.87; 95% CI 0.86- 0.88 for every increase of 0.26 mmol/l of total serum cholesterol concentrations), while statin use was associated with an increased risk (OR, 1.54; 95% CI 1.31-1.81 of the average level of total serum cholesterol)

- The protective effect of serum cholesterol against ICH was reduced by statins in strictly lobar brain regions more than in non-lobar regions

Pandit et al. Acta Neurol Scan. 2015 (Epub)

- Meta-analysis of 7 RCTs involving 31099 subjects receiving high-dose statin and 31105 placebo-treated patients to assess the association between higher dose of various statins and risk of ICH among patients with CVD

- A significant risk of ICH was observed in subjects with higher dose of statin (RR 1.53; 95% CI: 1.16-2.01; P = 0.002)

- There was no difference in all-cause mortality between the two groups (RR 0.95; 95% CI: 0.86-1.06; P = 0.36)
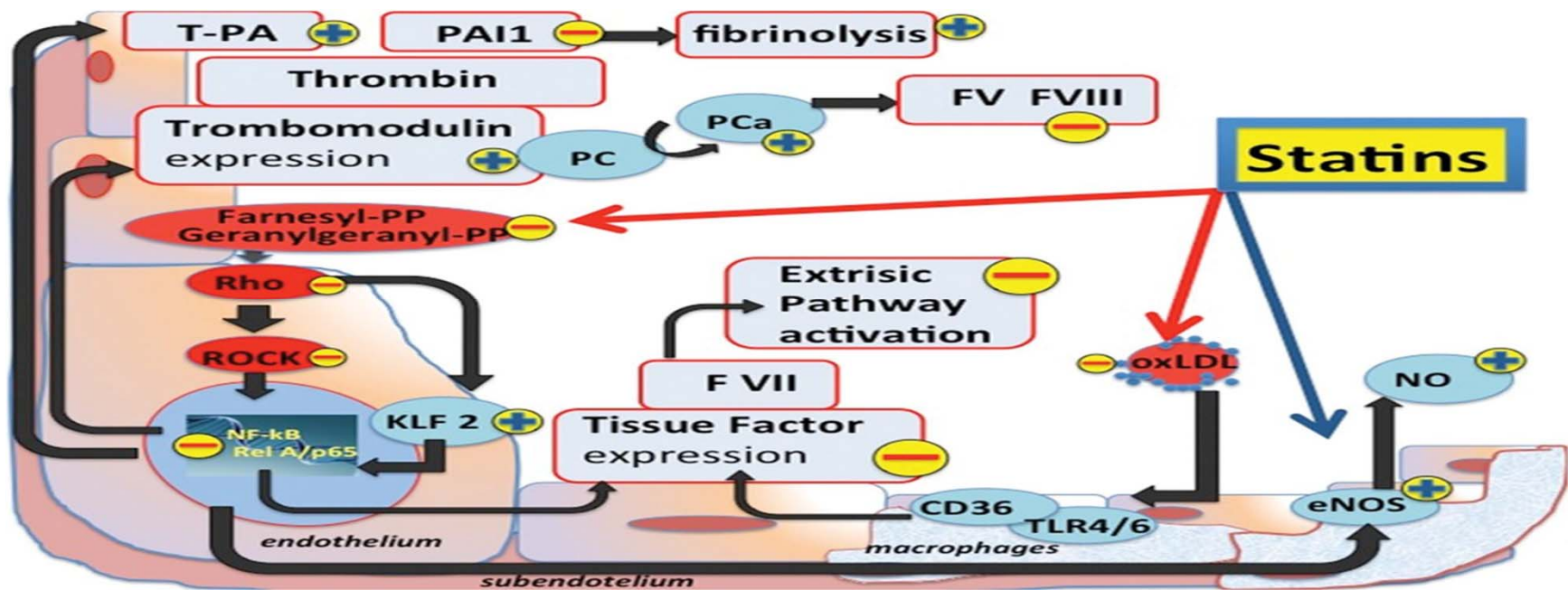
Statins might increase the propensity for ICH by inhibiting platelets, decreasing thrombus formation, and enhancing fibrinolysis

- There is insufficient data to recommend restrictions on use of statin agents (Class IIb; Level of Evidence: C).

- Class IIb = Usefulness/efficacy is less well established by evidence or opinion

- Level of Evidence C = Consensus opinion of experts, case studies, or standard of care

J. Claude Hemphill III, MD, MAS, FAHA, Chair; Steven M. Greenberg, MD, PhD, Vice-Chair; Craig S. Anderson, MD, PhD; Kyra Becker, MD, FAHA; Bernard R. Bendok, MD, MS, FAHA; Mary Cushman, MD, MSc, FAHA; Gordon L. Fung, MD, MPH, PhD, FAHA; Joshua N. Goldstein, MD, PhD, FAHA; R. Loch Macdonald, MD, PhD, FRCS; Pamela H. Mitchell, RN, PhD, FAHA; Phillip A. Scott, MD, FAHA; Magdy H. Selim, MD, PhD; Daniel Woo, MD, MS; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, and Council on Clinical Cardiology

Purpose—The aim of this guideline is to present current and comprehensive recommendations for the diagnosis and treatment of spontaneous intracerebral hemorrhage.

Methods—A formal literature search of PubMed was performed through the end of August 2013. The writing committee met by teleconference to discuss narrative text and recommendations. Recommendations follow the American Heart Association/American Stroke Association methods of classifying the level of certainty of the treatment effect and the class of evidence. Prerelease review of the draft guideline was performed by 6 expert peer reviewers and by the members of the Stroke Council Scientific Oversight Committee and Stroke Council Leadership Committee.

Results—Evidence-based guidelines are presented for the care of patients with acute intracerebral hemorrhage. Topics focused on diagnosis, management of coagulopathy and blood pressure, prevention and control of secondary brain injury and intracranial pressure, the role of surgery, outcome prediction, rehabilitation, secondary prevention, and future considerations. Results of new phase 3 trials were incorporated.

Conclusions—Intracerebral hemorrhage remains a serious condition for which early aggressive care is warranted. These guidelines provide a framework for goal-directed treatment of the patient with intracerebral hemorrhage. (*Stroke.* 2015;46:2032-2060. DOI: 10.1161/STR.0000000000000069.)

Key Words: AHA Scientific Statements ∎ blood pressure ∎ coagulopathy ∎ diagnosis ∎ intracerebral hemorrhage ∎ intraventricular hemorrhage ∎ surgery ∎ treatment

My Thoughts..

StATins Use in intRacerebral hemorrhage patieNts

SATURN
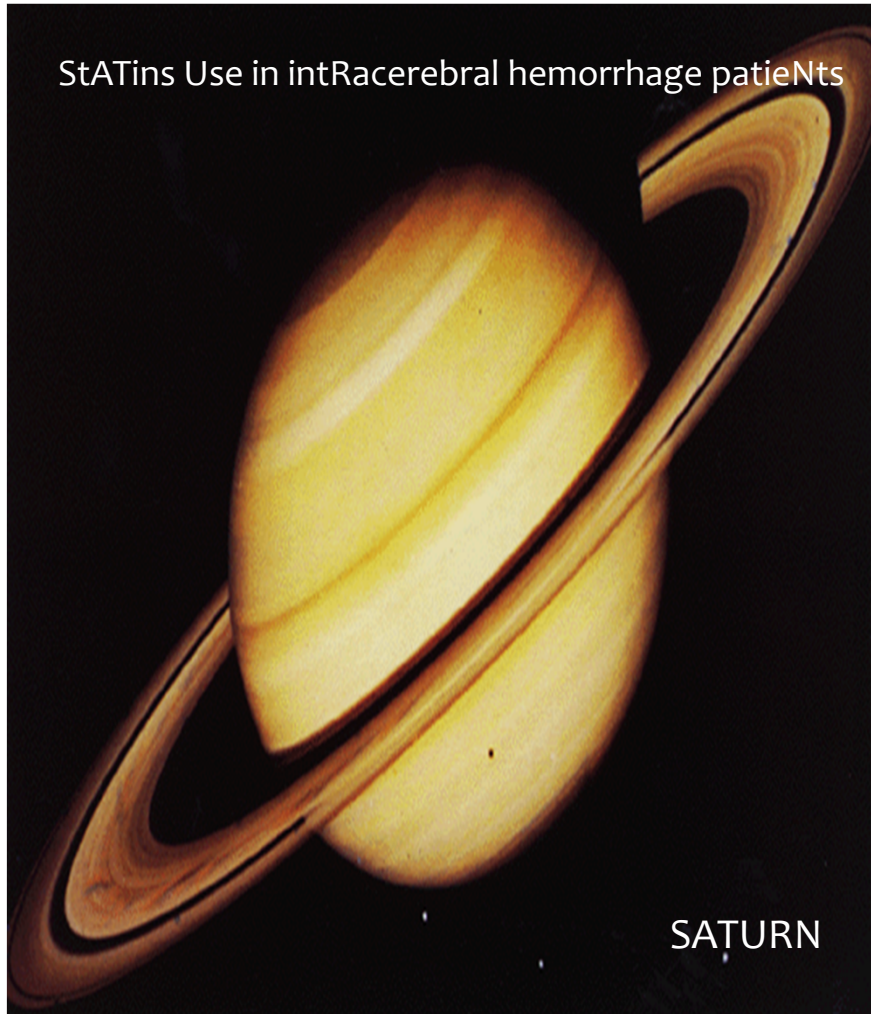
Coming soon …

o Avoid high dose statins

o Reserve for compelling indications, especially in patients with suspected CAA

o Minimize use with APLs!

o Avoid in those with recurrent lobar ICHs despite cessation of APLs and adequate BP control

Thank You